Multifunctional regulation of the biological effects of TNF-alpha by the soluble type I and type II TNF receptors.

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Abstract

Two soluble receptors of tumour necrosis factor were evaluated for development as potential therapeutic agents for inflammatory disease. The recombinant human soluble Type I and Type II TNF receptors, rsTNF-RI and rsTNF-RII, were expressed at high levels in E. coli, refolded, and chromatographically purified to homogeneity. The potencies of both recombinant soluble receptors were similar to their naturally occurring soluble receptors. In in vitro cytotoxicity and competitive binding assays, both recombinant soluble receptors functioned to inhibit the biological effects of rhTNF-alpha although rsTNF-RI was a 5 to 30 fold more potent inhibitor of rhTNF-alpha than was rsTNF-RII or a truncated form of the soluble receptor, TNF-RII delta. In in vivo experiments in mice, rsTNF-RI was a better inhibitor than rsTNF-RII delta of rhTNF-alpha-stimulated changes in the percentages of circulating lymphocytes and neutrophils, influx of neutrophils into the peritoneal cavity, and serum IL-6 induction. At molar ratios of 0.1:1 and 0.01:1 (rsTNF-R:rhTNF-alpha), using the rsTNF-I or rsTNF-II delta, there was a trend towards enhancement of the induction of IL-6. However, higher ratios of either rsTNF-RI or rsTNF-RII delta significantly inhibited the rhTNF-alpha-stimulated increase in serum IL-6 levels. In a murine model of cytokine-induced shock, either rsTNF-RI or rsTNF-RII delta provided protection against the lethality of shock induced by a synergistic combination of rhTNF-alpha and rhIL-1 beta. Based on the results of these experiments, the rsTNF-RI was chosen as the better candidate for development as an anti-inflammatory agent.

MeSH

Animal; Anti-Inflammatory Agents, Non-Steroidal; Ascitic Fluid; Base Sequence; Binding, Competitive; Cloning, Molecular; Comparative Study; Drug Synergism; Female; Human; Interleukin-1; Interleukin-6; L Cells (Cell Line); Leukocyte Count; Mice; Mice, Inbred BALB C; Mice, Inbred C57BL; Molecular Sequence Data; Neoplasm Proteins; Peptide Fragments; Receptors, Tumor Necrosis Factor; Recombinant Fusion Proteins; Shock;